January 31, 2002

Dr Gary Buehler
Food and Drug Administration
Division of Dermatologic & Dental Drug Products, HFD-600
Center of Drug Evaluation and Research
Metro Park North 2, Room 286
7500 Standish Place
Rockville, MD 20855

CONFIDENTIAL AND PROPRIETARY

Dear Drs Buehler, Galson, Bull and Seligman,

Re: NDA 18-662 - Accutane (isotretinoin) Capsules
Request for Meeting

We refer to our letter of November 5, 2001 (attachment 1) and the meeting with yourself and representatives from the Office of Generic Drugs (OGD), the Division of Dermatologic and Dental Products (DDDP) and the Office of Post Marketing Drug Risk Assessment (OPDRA) on December 5, 2001 to discuss issues relating to the potential public health consequences of having multiple isotretinoin products on the market. Roche identified several areas of concern that need to be addressed prior to the availability of multiple isotretinoin products including 1) public health surveillance (metrics); 2) healthcare provider and patient compliance with regard to which pregnancy prevention program they are participating in and 3) reproducibility of Roche's current program of education training and expertise.

At the meeting with representatives of the FDA on December 5, 2001, Roche understood the following:

- FDA agreed with Roche that the concerns raised were valid issues that needed to be addressed prior to entry of other products to the market place.
- FDA confirmed that no other isotretinoin product will be able to come to the market unless they fulfill the requirements for safety and meet the same rigid criteria as Accutane.
- Generic isotretinoin products will be required to have an identical pregnancy risk management program to the S.M.A.R.T. program which was approved October 30, 2001. The content of the program will be identical if it is considered labeling and any generic product will be required to carry the same educational components including training and 1800 numbers that are specified in Accutane labeling.
- Generic products will be required to adhere to the same metrics as agreed for Accutane. FDA agreed in principle with the goal to ensure ability to distinguish data from different risk management programs. However, ultimately FDA is interested in the global safety of the molecule.
- A central database containing data from all isotretinoin products may be an option. An independent body could be an option to ensure separation and non-duplication of data.
- Roche understood that the issue of whether prescriptions should bear a "dispense as written" or similar legend in order to facilitate linkage of a specific drug product to that manufacturer's risk management program still required discussion and resolution.
- FDA suggested a meeting between Roche and generic companies at a later stage to discuss how the shared public health issues could be resolved prior to other products coming to the market.

On January 30, 2002 Roche was advised informally by Dr. Allen Mitchell from the Slone Epidemiology Unit, Boston University School of Public Health that FDA has agreed that an "Isotretinoin Survey" will now be conducted with a common protocol, infrastructure, advisory committee and analytic approach for all isotretinoin products. Dr. Mitchell indicated that it is no longer feasible to conduct the "Accutane Survey", which we have spent recent months finalizing with FDA, and that FDA supported this approach.

Roche is concerned to receive this information from a third party and would like to understand why this information has not been communicated to Roche by FDA. We therefore request an urgent meeting with FDA within the next week to discuss how the public health issues which will affect both Accutane and other isotretinoin products have been resolved.

In particular we are concerned that:

- Roche has not been involved in any discussion between FDA and generics to discuss how to mutually resolve the public health issues as agreed at our meeting of December 5, 2001.
- Roche has not been provided with a primary FDA contact to follow up on issues relating to the public health consequences of multiple isotretinoin products being available.
- Roche had reached agreement through extensive discussions with FDA on the content and specifics of the Accutane Survey. We are due to implement this Survey in the near future and are concerned to be provided contrary information by a third party indicating that FDA may have adopted an alternate viewpoint with respect to the program.
- Roche is still in discussion with FDA on details of the Prescription Compliance Survey. We would like to discuss requirements for generics with respect to this component.
- Roche is in the process of finalizing with FDA the brochure entitled "Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Accutane (isotretinoin)." We would like to confirm that approval of this item will be viewed as labeling and understand what requirements will be applied in relation to this brochure for other products.
- Roche is discussing with FDA the details of a clinical study to assess psychiatric events. We would like to discuss requirements for other products in relation to such a study.

We are concerned that FDA may be moving forward without providing Roche with a meaningful opportunity to be heard on these complex issues, as clearly had been promised at our December 5 meeting. We would appreciate a response to this letter with immediate urgency and details of a primary contact at FDA who Roche can deal with in respect of these issues.

Sincerely

HOFFMANN-LA ROCHE INC.

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